

A Case Report: Intractable Epilepsy in a Child with Alpers-Huttenlocher Syndrome

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Abstract

Alpers-Huttenlocher syndrome is a progressive neurologic disorder that begins during childhood and is characterized by a clinical trial of progressive developmental regression, intractable seizure and liver degeneration. The prevalence of Alpers syndrome is approximately 1 in 100,000 individuals. Treatment is supportive and prognosis is poor. We report a case of Alpers syndrome in a child detected by clinical, biochemical and genetic testing.

Keywords: *Alpers-Huttenlocher Syndrome; Epilepsy; Neurologic Disorder*

Introduction

Alpers-Huttenlocher syndrome is a rare autosomal recessive mitochondrial DNA depletion syndrome with mutation in the POLG1 genes. Due to reduce synthesis of polymerase gamma, mitochondrial efficiency is reduced in organ of high energy demand like brain and liver. Bernard Alpers described this uncommon syndrome in a 4-month-old girl with normal developmental milestones, who later developed intractable seizures. Later Huttenlocher, *et al.* described the association of liver dysfunction and cerebrospinal fluid findings and established the inheritance as autosomal recessive. Alpers syndrome is usually characterized by a clinical trial of psychomotor retardation, intractable epilepsy and liver failure in infants and young children. The first peak age at onset reported in literature, is between age 2 - 4 years with a second at age 17 and 24 years. Infants and children with Alpers syndrome show no manifestations until the disease onset. We report a 12 months old child with intractable epilepsy and deranged liver enzymes in whom the diagnosis was confirmed by genetic testing [1-3,7].

Case Report

A 12 months old male child presented to ER with first seizure attack which lasted for one-hour duration. According to the mother he was in his normal state of health until this morning when he started repeated vomiting followed by jerky movement of the whole body with smacking of the lips and up rolling of the eyes. Parents mentioned he has been healthy with normal development till he got his first seizure. He was given status epilepticus protocol but his seizures continued and he was intubated and started on Iv midazolam and later levetiracetam was added to his treatment. He was discharged on levetiracetam and phenobarbitone with OPD follow up. His initial work up was normal except the EEG which showed a picture of focal epilepsy. A week later he was re admitted with another status epilepticus requiring PICU admission, Along with developmental regression, hypotonia and hemiplegia [5].

His blood workup was repeated and reported normal except Liver enzymes moderately elevated. His eye movements showed no limitation, and fundoscopic examination was normal. Visual evoked potential study was negative. MRI brain showed evidence of left mesial temporal sclerosis. His seizure became refractory to treatment with clonazepam, levetiracetam, phenobarbitone, topiramate, vitamin B6 and ketogenic diet. Virology panel for most common viruses e.g. CMV, herpes, EBV and varicella are negative. *Mycoplasma* IgM antibodies were negative. Further investigation with MR spectroscopy showed increased level of C4-DC and C3 in acylcarnitine profile. Decreased level of glutamine was detected in amino-acid profile. US abdomen: showing mild fatty changes of the liver. Genetic testing by whole exome sequencing revealed the presence of mutation in the POLG gene.

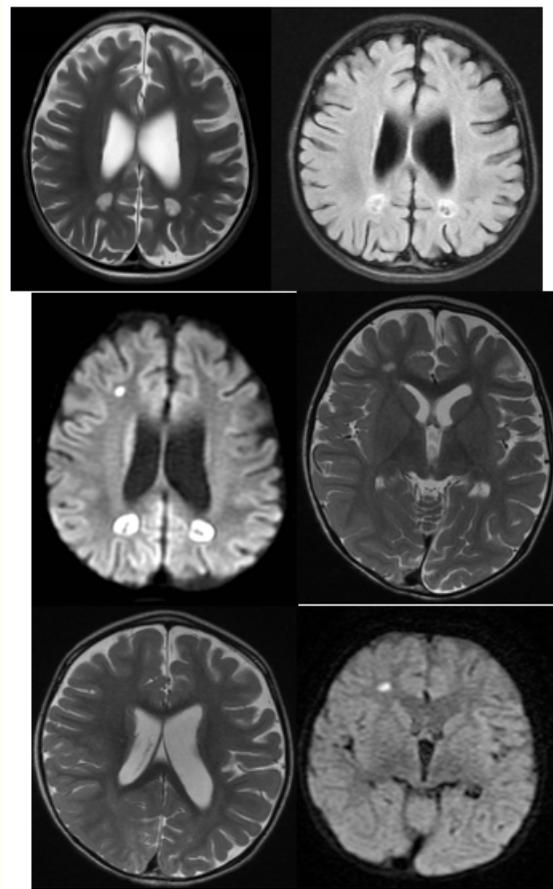


Figure: A- Small right frontal and left occipito-parietal recent lacunar infarcts.
B- Bilateral occipital cortical and subcortical signal changes could be due to old ischemic insult.
C- De-novo right frontal and bilateral parietal acute infarcts.
D- Right mesial temporal sclerosis.

Discussion

Alpers-Huttenlocher disease is the most severe form of POLG - related disorders. Less than 50 cases have been reported and affected individuals have the tendency of inheriting the genetic predisposition for the disorder. others may continue manifestation of primary

childhood disease. The Patho-genetics are not fully understood, however cytotoxic cerebral edema due to acute impairment of mitochondrial function could be one of the suggested mechanisms in Alpers syndrome. Electron transport chain and consequently impaired oxidative phosphorylation, oxidative stress and metabolic disturbances due to mitochondrial mutations or deletions is another possible mechanism evaluated previously.

Alpers syndrome must be included in the differential diagnosis of previously healthy children with seizures, impaired liver functions, microcephaly, abnormal EEG with (high-amplitude slow waves in combination with lower-amplitude poly-spikes), loss of visual evoked potentials and progressive brain atrophy on CT or MRI [1,7].

Histopathologic findings in Alpers syndrome are accumulation of lipids in the brain, microcystic lesions, spongiform degeneration with loss of neurons, reactive cortical gliosis and demyelination. Persistent Purkinje cells and loss of granular cells can be found in the cerebellar cortex and surroundings. The lesions can be unilateral or bilateral and mostly affect the occipital and parietal cortex, but cerebellum, brainstem, and basal ganglia are not spared. Thalamus, Hippocampus, substantia nigra and amygdala have extensive necrosis. CSF pleocytosis is often present. Neuroimaging findings shows cerebro-cortical involvement, with a predilection for the occipital lobes, and relative sparing of the white matter [3,4].

It is manifested by developmental regression, intractable seizures, spasticity, loss of DTR, ataxia, hearing and vision impairment, myoclonus, ataxia, nystagmus, hypotonia, partial paralysis and progressive dementia. Other rare feature are dysphagia, anemia and thrombocytopenia. The prognosis of Alpers syndrome is poor as it progresses to fatal encephalopathy, due to irreversible liver failure and results in early death in childhood. Uncontrolled seizures are another cause of poor prognosis.

Patients with Alpers disease have severe biochemical abnormalities of citric acid cycle, deficiency of pyruvate dehydrogenase, decreased utilization of pyruvate and decreased levels of cytochromes a and aa3. MR spectroscopy has proven to be more sensitive regarding lactate detection than neurometabolic examination of the serum and cerebrospinal fluid.

Treatment of Alper syndrome is supportive and directed to symptoms management. Older and Newer antiepileptic drugs shown similar efficacy in controlling seizures in AHS. Valproic acid is usually avoided due to risk of fulminant hepatic failure in children who may not have had hepatic involvement [3,7].

Ketogenic diet has shown effective in few patients. Liver failure need standard treatment for liver failure and Levocarnitine. Due to progressive neurocognitive impairment and multisystem organ involvement, liver transplantation is contraindicated [1].

Due to low 5-methyl-tetrahydrofolate in CSF suggested empirical treatment with calcium leucovorin that crosses the blood-brain barrier and increases cerebral folate has been tried. EPI-743 is a new drug that is based on vitamin E. Tests have shown that it can help improve the function of cells with mitochondrial problems and a hope in Alpers syndrome [3,7].

Conclusion

In summary, in our case the triad of psychomotor retardation, intractable epilepsy and liver failure is well-established criteria to make the diagnosis of Alpers-Huttenlocher syndrome. MRI brain findings of medial temporal sclerosis with progressive cortical lesions and infarction with low intensity in T1 weighted images support the diagnosis. we confirmed our diagnosis by WES (Whole exome sequencing) and revealed a POLG mutation, Parents testing were also done and confirmed the homozygosity of the mutation. Parents were counselled with advice regarding planning for future pregnancy and the need for prenatal diagnosis. Prompt diagnosis of AH syndrome is important to avoid drug-induced fulminant liver failure, particularly since liver transplantation is deemed inappropriate due to the short life expectancy of these patients.

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